REMARKS

Claims 1, 2, 6-9, 11, 13, 14, 16, 25, 26, 29, 30, 32, 33 and 102 are currently pending in the present application. Claims 5, 12, 28 and 46-49 have been withdrawn by the Examiner as drawn to a non-elected species. Applicants reserve the right to rejoin these claims when a generic claim is allowed. Claims 1, 16 and 25 are amended to no longer recite "proliferation". New claims 103-120 are added, which are drawn to methods of modulating proliferation of a hematopoietic stem or progenitor cell, or a pharmaceutical composition that modulates proliferation of a hematopoietic stem or progenitor cell. Claim 11 is canceled herein and replaced with new claims 103 and 104. New claims 105-109 and 111-120 correspond to present claims 1, 6, 7, 8, 9, 13, 14, 16, 25, 26, 29, 30, 32 and 33, respectively. New claims 110 and 111 correspond to new claims 103 and 104, respectively. After entry of the present Amendment, claims 1, 2, 6-9, 13, 14, 16, 25, 26, 29, 30, 32, 33 and 102-120 will be pending.

I. Withdrawn Claims 5, 12, 28 and 46-49 Should Be Rejoined

The Examiner has withdrawn claims 5, 12, 28 and 46-49 from consideration as being drawn to a non-elected species ("differentiation in cell culture"; *see* August 4, 2006 Office Action at page 4; December 6, 2005 Office Action at page 5). The Examiner has rejected the claims as obvious over art that ostensibly discloses only contact between a PDE4 inhibitor and a stem or progenitor cell *in vitro*. As such, the Examiner is treating "differentiation *in vivo*" and "differentiation *in vitro*" as not patentably distinct, that is, having unity of invention. As such, Applicants respectfully request that the Examiner withdraw the species election requirement with respect to location of differentiation (*see* June 10, 2005 Restriction Requirement at page 3) and rejoin claims 5, 12, 28 and 46-49 for examination. Alternatively, if the Examiner maintains that contacting *in vitro* and contacting *in vivo* are patentably distinct, the Examiner is respectfully requested to state on the record that claims limited to contacting *in vivo* are allowable.

I. The Rejection Under 35 U.S.C. § 112, First Paragraph, Should Be Withdrawn

Claim 11 remains rejected under 35 U.S.C. § 112, first paragraph, as allegedly being non-enabled. Advisory Action at page 3. The Examiner alleges that claim 11 "is not limited to differentiating $CD34^+$ cells to $CD33^+$ cells; the claims allows that the cells may be $CD33^-$." *Id.* Without conceding the propriety of the Examiner's rejection, Applicants have

canceled claim 11 and added new claims 103 and 104. New claim 103 specifies that the stem or progenitor cell of claim 9 is $CD34^+$. New claim 104 re-presents canceled claim 11. Thus, according to new claims 103 and 104, it is a $CD34^+$ cell that differentiates into a $CD34^+CD38^-CD33^+$ cell.

New claim 104 is enabled. The $CD34^+$ cells from which the cells differentiate are well-known, as are methods of obtaining them. Causing the $CD34^+$ cells to differentiate is straightforward, as conditions for differentiation of $CD34^+$ stem cells are well-known, and the claim requires only contacting the $CD34^+$ cells with the specific compound recited in claim 1. As pointed out by the Examiner, Example 11 explains how to facilitate the claimed modulation of differentiation. Selection of the amount of compound would be, as pointed out by the Examiner, "a routine matter of optimization". *See* Office Action mailed August 4, 2006 at page 9, lines 13-14 and page 12, line 21 to page 13, line 1. As such, the specification clearly lays out how to accomplish the method of claim 104.

For the above reasons, it is respectfully requested that the rejection of claim 11 under 35 U.S.C. § 112, first paragraph, be withdrawn.

III. The Rejections Under 35 U.S.C. 103(a) Should Be Withdrawn

The Examiner has rejected the claims over several combinations of references. Each is discussed in turn below.

The Rejection Over Elsas, Muller and Janowska

Claims 1, 2, 7-9, 16, 25, 26, 29, 30, 32, 33 and 102 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Gaspar Elsas *et al. (British Journal of Pharmacology* 130:1362-1368 (2000), hereinafter, "Elsas") in view of Muller (U.S. Patent 6,020,358, hereinafter, "the '358 patent") and Janowska-Wieczorek *et al.* (*Blood* 98:3143-3149 (2001), hereinafter, "Janowska"). Janoswka is cited solely as evidence mouse bone marrow comprises $CD34^+$ and $CD11b^+$ cells. August 4, 2006 Office Action at page 8. In particular, the Examiner contends that a person of ordinary skill in the art would have had a reasonable expectation of success in substituting the compound used by Muller into the method of Elsas, as the compounds used by Muller and Elsas are PDE IV inhibitors.

It is a well-established legal principle that a finding of obviousness requires that the prior art both suggests the invention and provides one of ordinary skill with a reasonable expectation of success. *DyStar Textilfarben GmbH & Co. Deutschland KG v. C.H. Patrick Co.*, 464 F.3d 1356 (2006); *In re O'Farrell*, 853 F.2d 894 (Fed. Cir. 1988). In the instant

case, the cited art and common knowledge in the relevant art fails to teach or suggest the invention as claimed in the amended claims, and fails to provide a person of ordinary skill in the art with a reasonable expectation of success, as explained below.

The claims as amended are drawn to a method for modulating the proliferation or differentiation of a mammalian hematopoietic stem cell or hematopoietic progenitor cell to a blood cell by contacting with an PDE4 inhibitor of a specific structure. Elsas allegedly teaches that different compounds including rolipram (a PDE4 inhibitor) are capable of modulating a degree of colony formation by hematopoietic stem cells of mouse bone marrow. Elsas does not teach contacting hematopoietic stem cells or hematopoietic progenitor cells with a compound of structure VII, as claimed.

The Examiner contends that Muller teaches the compound of structure VII and that, because the compound of structure VII and rolipram are both PDE4 inhibitors, a person of skill in the art would have a reasonable expectation of success in substituting the compound of structure VII for rolipram in the method of Elsas. August 4, 2006 Office Action at page 9, lines 3-5. However, the Examiner has characterized the present invention as part of "an unpredictable art" (December 6, 2005 Office Action at page 12, line 3). The Examiner is respectfully reminded that unpredictability must be considered in determining obviousness, M.P.E.P. Eighth Edition, Incorporating Revision No. 5, 2144.08(II)(A)(4)(e), at page 2100-149, and that the unpredictability in question regarding the pending claims is the unpredictability of the effect of a compound on *differentiation*, not simply cAMP levels. Because the genus of PDE4 inhibitors is large and varied, a person of skill in the art cannot predict with any confidence whether one member of the genus will have an effect equivalent to another member on differentiation of a stem cell. As such, a person of ordinary skill in the art would not have a *reasonable* expectation of success in combining Elsas and Muller to achieve the claimed method.

Moreover, Muller suggests that the compounds described therein could be used for the treatment of *disease*, particularly viral disease. *See* the first three paragraphs of column 7. This intended use is far removed from the modulation of differentiation or proliferation of a stem cell. Thus, a person of ordinary skill in the art would not be motivated to combine Muller with the remaining references to produce the claimed invention.

The Examiner, quoting *DyStar*, states that "the motivation to substitute one compound for another with the same function can be found in the common knowledge of the art and common sense of its skilled practitioners." Office Action at page 4. "Rejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must

be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *KSR v. Teleflex*, No. 04-1350, *slip. op.* at page 14 (U.S. 2007), citing *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006). Assertions of "common knowledge" and "common sense" are mere conclusory statements because they do not explain, for example, *what* common knowledge is implicated, nor from what knowledge the common sense arises. As such, they are insufficient to support a *prima facie* case of obviousness.

The Examiner should bear in mind that the invention in *KSR*—a throttle control—and the invention in *DyStar*—a process for dyeing textiles—are both technically simple and involve completely predictable, controllable parameters (*e.g.*, the location of a sensor on a throttle). The present invention, however, involves cells, which are far more complex biochemical machines, a fact of which the person of ordinary skill in the art is acutely aware. In fact, there is nothing in either of Elsas or Muller that teaches or suggests, and no understanding in the common knowledge or common sense of the skilled practitioners in the art, that compounds that generally have a function—PDE4 inhibition—in common would likewise have equivalent effects on the differentiation of a stem or progenitor cell. Given the inherent variability of effect between and among PDE4 inhibitors, common sense would, at best, only encourage a person of ordinary skill to *try* substituting the compound of formula VII for rolipram in the method of Elsas. However, "obvious to try" has never been the standard for a determination of obviousness. The Supreme Court stated that when "there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the *known options* within his or her technical grasp." *KSR International Co. v. Teleflex Inc.*, 550 U.S. ___ (Slip. Op. at 17) (emphasis added). Here, the option of the compound recited in the pending claims, for differentiation of stem cells, was not known prior to the filing date of the present application. Moreover, unlike the simple throttle controls at issue in *KSR*, the activities of various members of the class of PDE4 inhibitors on the differentiation of stem or progenitor cells is *not* predictable, and neither Elsas nor Muller, nor any other source in the art, teaches or suggests that they are.

For the above reasons, Applicants maintain that the claims as amended are not obvious over Elsas, Muller and Janowska. Applicants respectfully request that the Examiner withdraw this rejection of the claims.

The Rejection Over Elsas, Muller, Janowska and Waki

Claims 1, 2, 7-9, 11, 13, 14, 16, 25, 26, 29, 30, 32, 33 and 102 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Elsas in view of Muller and

None of the references, however, teaches or suggests the modulation of differentiation of a hematopoietic stem or progenitor cell into a blood cell, as required by the amended claims. Waki only discloses that XT-44 administration appears to result in a higher bone mineral density. Such an effect is attributed in Waki to an inhibition by XT-44 on osteoclastogenesis. *See, e.g.*, page 481, right column, second paragraph. Waki also *assumes* that PDE4 inhibitors could stimulate osteoblastic differentiation. Page 481, right column, first paragraph. Osteoclasts and osteoblasts, however, are bone cells, not blood cells, as required by the amended claims. Both Muller and Janowska fail to remedy this deficiency in Waki. Thus, the combination of Waki, Muller and Janoswka fails to teach all of the limitations of the claims as amended. For this reason, a person of ordinary skill in the art would not have a reasonable expectation of combining the cited references to produce the claimed method.

For the above reasons, Applicants maintain that the claims as amended are not obvious over Elsas, Muller and Janowska. Applicants respectfully request that the Examiner withdraw this rejection of the claims.

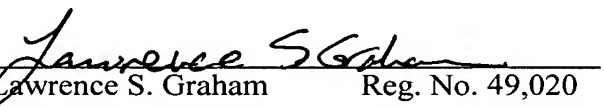
CONCLUSION

Applicants respectfully request that the present remarks be made of record in the file history of the present application. An early allowance of the application is earnestly requested. The Examiner is invited to contact the undersigned with any questions concerning the application.

No fee, other than an extension of time fee, is believed to be due in connection with this response. However, the Commissioner is authorized to charge all required fees, fees under 37 C.F.R. § 1.17 or credit any overpayment, to Jones Day U.S. Deposit Account No. 503013, referencing Attorney Docket No. 9516-149-999 (CAM: 501872-999148).

Respectfully submitted,

Date: June 15, 2007



by: Lawrence S. Graham Reg. No. 49,020
for: Anthony M. Insogna Reg. No. 35,203

JONES DAY
222 East 41st Street
New York, NY 10017-6702
(212) 326-3939